REMARKS

Amendments

Claims 1, 11, 12, 15 and 16 have been amended. Claims 2 and 14 have been cancelled. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Priority

The paragraph on page 1, line 12 of the specification has been amended to include the correct benefit of priority based on provisional patent application U.S. Serial number 60/215,960, filed July 5, 2000.

35 U.S.C. §112, first paragraph

Claims 1, 3-4, 11-13, 15-16 are rejected under 35 U.S.C. 112, first paragraph, for being non-enabling. The rejection is respectfully traversed.

The Examiner contends that the specification while being enabling for the cascade of functions in claims 2 and 14, does not reasonably provide enablement for any and all cell functions. The specification does not enable any person skilled in the art to which it pertains to use the invention commensurate in scope with claims 1, 3-4, 11-13 and 15-16.

Claim 1 has been amended to include the limitations of claim 2 and claims 11 and 15 have been amended to include the limitations of claim 14. Claims 2 and 14 are accordingly cancelled. In light of the amendments to claims 1, 11 and 15, Applicants respectfully submit that claims 1, 3-4, 11-13 and 15-16 find support in the specification and a person of ordinary skill in the art could make and use the invention commensurate in scope with the claims.

35 U.S.C. §112, second paragraph

Claims 1-4 and 11-16 are rejected under 35 U.S.C. 112, second paragraph as being indefinite.

The Examiner needs clarification on whether claims 1-4 is *in vivo* or *in vitro*. Claim 1 has been amended to specify *in vitro* treatment.

Claims 1-4 and 15-16 were deemed not to recite an effective amount. Claim 4 does recite an effective concentration range of ascorbic acid from about 0.05 mM to about 0.5 mM. Claim 15 has been amended to recite the same concentration range of ascorbic acid.

In claims 11 and 15, the word "such" was considered confusing as to the scope of its intent. Further, the word "treatment" was deemed to have no antecedent basis. Claims 11 and 15 have been amended to exclude the word "such" immediately preceding the word "treatment." The word "treatment" no longer needs antecedent basis after this amendment.

Claim 15 was considered as lacking support for the recitation of the "ophthalmic composition of claim 5" since claim 5 is withdrawn. Claim 15 has been amended to recite an ophthalmic composition of ascorbic acid in an acceptable pharmacological carrier.

The Markush list of intended injury and diseases of claim 16 was deemed confusing. Claim 16 has been amended to eliminate the parentheses and to illustrate conjunctivitis and diabetes mellitus as examples of diseases involving over-production of collagen and rheumatoid arthritis as an example of a disease involving under

production of collagen. The reference to "alkali burns" has been removed in view of a cited prior art (See *infra* under 35 U.S.C. §103(a)).

Lastly, claims 15 and 16 are deemed not to have antecedent basis for the recitation "eye diseases." Claim 15 is amended to include the recitation "eye diseases" to provide the antecedent basis for "eye diseases" in claim 16.

35 U.S.C. §103(a)

Claims 1-4 and 11-16 are rejected under 35 U.S.C §103(a) as being unpatentable over **Fahim** (U.S. Patent No. 4,711,780), **Rath** (U.S. Patent No. 5,230,996), **Saika** (abstract, 1993), **Nowak** (abstract, 1997) and **Nowak** (abstract, 2000) alone or in combination. The rejection is respectfully traversed.

The Examiner contends that each of the above cited references discloses that ascorbic acid phosphate and ascorbic acid promote recovery of cellular functions and wound healing such as proliferation following injury, including eye injury caused by a variety of conditions and injury caused by toxic substances. The Examiner contends that the claims of the present invention differ over the

references in reciting ascorbic acid concentration and a specific toxic substance and that once a method of using a compound is known to treat injury, no unobviousness is seen in an injury caused by a specific toxic substance. Applicants respectfully disagree.

The claimed invention teaches the systemic treatment of injured epithelial cells with pharmacological doses of ascorbic acid phosphate after exposure to injury such as the chemical dichlorovinyl-L-cysteine, specifically recovery of cellular functions such as proliferation, mitochondrial function, Na^+-K^+-ATPase protein expression and activity and active Na^+ transport. Examples given in the specification include data showing renal proximal tubular cell recovery and regeneration through recovery of cellular functions such as proliferation, mitochondrial function, Na^+-K^+-ATPase protein expression and activity and active Na^+ transport.

Fahim teaches the treatment of conditions involving surface epithelial inflammation with an pharmaceutical preparation of Vitamin C in combination with a mucosaccharide, a polysaccharide, zinc sulfate and a sulfur amino acid. Most of the data in **Fahim** involve topical treatment of burns, vaginitis, balantitis and itching caused by poison ivy and insect bites with such a concoction. In two

examples, the Vitamin C *plus* preparation is used to treat urethra infection and schistosomiasis. Furthermore, **Fahim** teaches the therapeutic value of the mucosaccharide, the polysaccharide, zinc sulfate and the sulfur amino acid. **Fahim** does not teach or suggest the systemic treatment of cell regeneration with solely Vitamin C after injury such as exposure to a toxin.

Rath teaches the reduction of lipoprotein binding to blood vessel explants specifically prior to surgery or generally to prevent atherosclerosis and other cardiovascular diseases with a solution of ascorbate and tranexamic acid. **Rath** does not teach nor suggest the recovery and proliferation of cell regeneration after injury by treatment with ascorbic phosphate.

Applicants respectfully submit that the **Nowak** abstract (2000) was published after the filing of the instant application and therefore is not prior art.

Nowak (abstract 1997) teaches regeneration of renal cells following exposure to tert-butylhydroperoxide by treatment with ascorbic acid. However, renal proximal tubular cells have the capacity to restore their structure and functions after sublethal injury caused by tert-butylhydroperoxide exposure even without ascorbic acid

treatment injury (Specification, page 5, line 16 to line 20). On the other hand, renal cells do not recover physiological functions from dichlorovinyl-L-cysteine induced injury (Specification, page 5, line 20 to page 6, line 3). The nature of the toxin actually determines the chances of cell recovery. Therefore, it was not obvious that once a method of using ascorbic acid was known to treat renal cells injured by tert-butylhydroperoxide, that it would be obvious to treat renal cell injury caused by dichlorovinyl-L-cysteine by ascorbic acid as well, particularly because self-recovery of cellular functions was observed in the tert-butylhydroperoxide exposed cells.

not rejected

Saika teaches the treatment of alkali burns in rabbit corneas using ascorbic acid phosphate. Claim 16 of the present invention teaches the treatment of cellular injury of the eye such as in cases of alkali burns with ascorbic acid phosphate. Claim 16 is amended to exclude the treatment of alkali burns with ascorbic acid phosphate.

- specific injury included in 1 + 15

In view of the absence of teaching of **Fahim, Rath, Saika** and **Nowak** that recovery of cellular function such as proliferation, mitochondrial function, Na^+-K^+-ATPase protein expression and activity and active Na^+ transport occurs after cellular injury by treatment with

ascorbic acid alone, Applicants submit that this invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. The references in combination do not provide a person having ordinary skill in this art with a reasonable expectation of success in producing Applicants' claimed methods. Accordingly, Applicants respectfully request that the rejections of claims 1-4 and 11-16 pursuant to 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed March 20, 2002. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: July 22, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph starting on page 1, line 12 has been replaced as follows:

--This non-provisional patent application claims benefit of priority of provisional patent application U.S. Serial number ~~60/212,224 filed June 15, 2000~~ 60/215,960 filed July 5, 2000, now abandoned.--

IN THE CLAIMS

Claim 1 has been amended as follows:

1. (Amended) A method of recovering cellular functions *in vitro* in cells following injury, comprising the step of:

contacting said cells with ascorbic acid or a salt of ascorbic acid~~.~~,

wherein said cellular functions include proliferation, mitochondrial function, Na^+-K^+-ATPase protein expression, Na^+-K^+-ATPase protein activity, and active Na^+ transport.

Claim 2 has been cancelled.

Claim 11 has been amended as follows:

11. (Amended) A method of recovering cellular functions following injury in an individual in need of ~~such~~ treatment, comprising the step of:

administering a therapeutically effective amount of ascorbic acid or a salt of ascorbic acid to said individual~~.~~, wherein said cellular functions include proliferation, mitochondrial function, Na^+-K^+-ATPase protein expression, Na^+-K^+-ATPase protein activity, and active Na^+ transport.

Claim 12 has been amended as follows:

12. (Amended) The method of claim 11, wherein said injury is selected from the group consisting of halogenated hydrocarbons-induced nephrotoxicity, ischemia-induced acute renal failure, ~~and~~ drug-induced acute renal failure, ~~and~~ glomerulonephritis, ~~and~~ skin abrasions, cuts~~,~~ and burns.

Claim 14 has been cancelled.

Claim 15 has been amended as follows:

15. (Amended) 15. A method of recovering cellular functions in eye diseases or following injury to ~~the~~ eye of an individual in need of ~~such~~ treatment, comprising the step of:

administering ~~the~~ an ophthalmic composition comprising a therapeutically effective amount of ascorbic acid or a salt of ascorbic acid in an ophthalmically acceptable carrier ~~of claim 5~~ to said individual~~,~~ wherein said cellular functions include proliferation, mitochondrial function, Na^+-K^+-ATPase protein expression, Na^+-K^+-ATPase protein activity, and active Na^+ transport and wherein said ascorbic acid is in the concentration range of from about 0.05 mM to about 0.5 mM.

Claim 16 has been amended as follows:

16. (Amended) The method of claim 15, wherein said injury is selected from the group consisting of acute injury to the eye, eye diseases associated with the over production of collagen as in ~~(~~conjunctivitis~~,~~ and diabetes mellitus~~)~~, and eye disease associated with the under production of collagen as in ~~(alkali burns,~~ rheumatoid arthritis~~)~~.